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Incidence and Spectrum of Renal Abnormalities in Williams-Beuren Syndrome

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Kidneys and urinary tract were examined systematically by ultrasonography in 130 patients with Williams-Beuren syndrome (59 females, median age 5.5 years; 71 males, median age 6.4 years). In addition, serum creatinine was determined and an analysis was performed. Creatinine clearance was available in 79 patients. Renal angiographic examinations were done in 18 patients, 8 of whom had renal artery narrowing (44%). The incidence of renal anomalies in Williams-Beuren syndrome was 17.7% vs. around 1.5% in the normal population ($P < 0.0003$). The spectrum of these anomalies ranged from minor anomalies such as bladder diverticula to more severe malformations such as renal aplasia or hypoplasia (in 5 of 130 patients). In nine patients a duplicated kidney was found. A decreased creatinine clearance (two patients), recurrent symptomatic urinary tract infections (four patients), and hypertension were uncommon. Nephrocalcinosis was not found in our patients. Our data demonstrate that the risk of a structural abnormality of the kidneys and the urinary tract is increased 12- to 36-fold in Williams-Beuren syndrome compared to the normal population. Ultrasound screening of the renal system should be part of the first evaluation of WBS patients.
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INTRODUCTION

Williams-Beuren syndrome (WBS) is a contiguous gene syndrome. A hemizygous deletion on the long arm of chromosome 7 (7q) was demonstrated [Ewart et al., 1993]. Besides developmental delay, cardiovascular lesions (typically supravalvular aortic stenosis and peripheral pulmonary stenosis), growth retardation, and a characteristic facial appearance, renal abnormalities are thought to be part of the syndrome. A variety of renal anomalies, both structural and functional, has been described in some case reports [Page et al., 1969; Bruns 1968, Biesecker 1987; Ino et al., 1988] and two small series of WBS patients [Stoermer et al., 1984; Ingelfinger and Newburger, 1991]. An estimation of the incidence and a definition of the spectrum of anomalies found in the syndrome is not reliably possible by these reports. Recently, Pober et al. [1993] reported on renal findings in 40 individuals with WBS. In a prospective study of 130 patients we systematically investigated the urinary tract to delineate the spectrum and the incidence of anomalies in WBS.

PATIENTS AND METHODS

Between 1989 and 1995 we investigated 59 WBS females at a median age of 5.5 years (range 0.1 to 47 years) and 71 WBS males with a median age of 6.4 years (range 0.7 to 33 years). Included in these two groups are 15 men (age 18 to 33 years) and 7 women (age 18 to 47 years). All patients presented with developmental delay, distinctive facial traits, and a behaviour phenotype as described by Dilts et al. [1990], Gosch et al. [1994], and Gosch and Pankau [1994]. The spectrum of cardiovascular anomalies was similar to that described by Wessel et al. [1994]. Kidney structure was evaluated by ultrasonography. Renal function was assessed by routine urinalysis and measurement of serum creatinine. In 79 patients a baseline creatinine clearance study was performed. In case of a pathological or suspicious finding on ultrasonography patients were investigated further by an iv pyelogram and/or a voiding cystourethrogram. The detailed medical history obtained in all 130 patients included recurrent urinary tract infections. In 18 patients an abdominal angiographic roentgenogram was obtained during cardiac

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catheterisation. Statistical comparisons between observed frequencies of malformations and those of the normal population were made by Fisher's exact test.

RESULTS

Of the 130 patients investigated in this study 23 had abnormal renal findings (17.7%). The spectrum of anomalies of the urinary tract is given in Table I. It is of importance to note that unilateral renal agenesis was found in five patients (3.8%); nine patients presented with a kidney duplication (6.9%). A vesicoureteral reflux was found in five patients (3.8%). Ultrasonography was suspicious of a bladder diverticulum in a further patient. Recurrent symptomatic urinary tract infections occurred in only four patients (3.1%). Laboratory examinations (urinalysis, serum creatinine, creatinine clearance) were normal in all but two patients (13.6-year-old girl, creatinine clearance reduced to 91 ml/min x 1.73 ^{2} vs. normal range: 124–149 ml/min x 1.73 m^2; 24-year-old man, creatinine clearance 91 ml/min x 1.73 m^2 vs. normal range: 94–140 ml/min x 1.73 m^2). Renal sonography and 24 hour blood pressure monitoring were normal in the girl. Abdominal angiography performed during cardiac catheterization showed renal artery narrowing in six patients (4.8%). In a female patient a ureteropelvic junction obstruction was corrected surgically at age 9 months. The ultrasound findings at age 14.2 years were normal and so was her blood pressure. In an 11-month-old boy with WBS antireflux surgery was performed because of hydronephrosis and megaureter on the left side. Ultrasound follow-up showed normal findings at age 2.7 years. Serum creatinine was normal. In a second boy surgical antireflux treatment was done at age 12 years after recurrent pyelonephritis. Control ultrasonography at age 24 years showed a duplicated renal pelvis on the left side in addition to severe renal scarring; 24 hour blood pressure monitoring revealed a borderline arterial hypertension. Serum creatinine and creatinine clearance were normal. Renal hypoplasia on the right side was demonstrated on ultrasonography in a 5.4-year-old boy. The iv pyelography confirmed this finding. However, renal function and blood pressure were normal. During cardiac catheterization at age 1.7 years findings compatible with a duplicated kidney on the right side were noted in a WBS girl. Serum creatinine was normal. Further diagnostic procedures were refused by the parents. On single measurements blood pressure was generally normal except for one man (age 24 years) showing borderline arterial hypertension as mentioned above. On ultrasound examination renal echogenicity was normal in all patients.

TABLE I. Spectrum of Renal Malformations and Diseases in 130 Patients With Williams–Beuren Syndrome

Renal abnormality	Number of patients	(%)
Renal agenesis	5	3.8
Renal hypoplasia	1	0.8
Duplicated kidney	9	7
Horseshoe kidney	1	0.8
Dystopic kidney	2	1.5
Renal artery stenosis	8	6.2 (44.4)[a]
Hydronephrosis and megaureter	1	0.8
Stenosis of ureteropelvic junction	1	0.8
Bladder diverticulum	1	0.8
Recurrent urinary tract infections	4	3.1
Vesicoureteral reflux	5	3.9

[a]Percentage calculated from number of patients with angiographical evaluation (n = 18).

DISCUSSION

In part of the textbook literature on syndromes [Buyse, 1990; Gorlin et al., 1990; Leiber and Olbrich, 1990] no statement is made about the frequency and the spectrum of renal malformations and anomalies in WBS. Jones [1988] and Wiedemann and Kunze [1995] mention the association of renal malformations with WBS. Leiber and Olbrich [1990] describe renal "dysplasia" as associated malformation. Thus, there is a clear need for more and better information of the renal system in WBS. In the study of Wesselhoeft et al. [1980] renal anomalies are listed in only 2 of 79 patients (2.5%). However, it has to be assumed that this group of patients was not screened systematically for renal anomalies. In 65 patients with congenital cardiac and renal malformations one child also had the WBS [Bruns, 1968]. Morris et al. [1988] reported three patients with vesicoureteral reflux. These authors noted that the incidence of renal anomalies in WBS is unknown. However, a first report on the frequency of renal findings was done by Stoermer et al. [1984] who found anatomical abnormalities of the kidneys in 11 of their 14 patients (78.6%). Côté et al. [1989] performed ultrasound examinations of the kidneys in 25 children and adolescents with WBS. In five patients (20%) an increased echogenicity of the renal parenchyma indicating nephrocalcinosis was found. Hypercalcemia during infancy was documented in two of these five patients. On the other hand, children with normal serum calcium levels during the first year of life did not develop nephrocalcinosis during further follow-up. In our series of 130 WBS patients we did not find a single patient with increased renal echogenicity on ultrasonographic examination. Hypercalcemia in infancy was documented in two of our patients only (1.5%).

Ingelfinger and Newburger [1991] reported renal agenesis in 2 of 27 patients (7.4%). Additional renal anomalies were noted in another 11 patients (40.7%). In 3 of 13 adults with WBS Morris et al. [1990] found vesicoureteral reflux, urethral stenosis, and diverticula of the bladder. Pober et al. [1993] were the first to investigate systematically the kidneys and the urinary tract in a larger series of WBS children (n = 40). Seven (18%) showed abnormal findings (Table II). The 18% frequency of renal anomalies is in accordance with that in our series (23 of 130; 17.7%). The spectrum of abnormal findings ranged from minor anomalies such as bladder diverticula to more severe malformations such as renal agenesis or renal hypoplasia. Three patients had undergone surgical treatment of stenosis of the uretero-pelvic junction and hydronephrosis during infancy or childhood. One of these showed severe renal scarring on a follow-up examination.

TABLE II. Review of the Literature Dealing With Renal and Urinary Tract Abnormalities in Williams–Beuren Syndrome

Reference	Year of publication	Number of pts	Renal abnormalities	Renal aplasia	Renal hypoplasia	Kidney duplication	Horseshoe kidney	Kidney dystoplia	Stenosis of ureteral Pelvic junction	Vesicoureteral reflux	Nephrocalcinosis	Renal artery narrowing/stenosis	Functional abnormality[a]	Renal cyst	Duplicated pelvis
Wesselhoeft et al.	1980	79	2[b] (2.5)	–	–	–	–	–	–	–	–	–	–	–	–
Stoermer et al.	1984	14	12 (85.7)	–	–	3	–	1	–	2	1	3	–	1	2
Côté et al.	1989	25	5 (20)	–	–	–	–	–	–	–	5	–	–	–	–
Ingelfinger and Newberger	1991	32	11/27 (41)	2/27	–	–	1/27	–	–	–	–	8/15	3/30(fct.↓)	–	–
Pober et al.	1993	40	7 (17.5)	1	1	–	–	1	–	1	2	5/9	2	–	–
Present study	**1996**	**130**	**23 (17.5)**	**5**	**1**	**9**	**1**	**3**	**1**	**5**	–	**8/18**	**2**	–	–
Total	–	320	60	8	2	12	2	5	1	8	8	24	7 (12)	1	2

[a]Functional abnormalities: abnormal findings in urinalysis, serum creatinine, or creatinine clearance.
[b]Further information not available.

An increased frequency of renal aplasia is found in WBS. The prevalence of this abnormality is 0.2% in the normal population [Gruenwald, 1943] and about 3.8% in WBS patients (5 of 130). Thus, the relative risk for renal aplasia in WBS is increased 20-fold in comparison to the normal population ($P < 0.0003$). A comparably high relative risk (7.4%) was reported by Ingelfinger and Newburger [1991].

The prevalence of renal malformations in children is generally reported to be 0.5 to 1.5% [Sheih et al., 1989, Steinhart et al., 1988]. On the basis of our results in the largest series of WBS patients reported so far the frequency of renal abnormalities is 17.7%. A nearly identical frequency was reported by Pober et al. [1993]. Thus, the risk of renal abnormalities in WBS is increased 12- to 36-fold compared to the normal population ($P < 0.00001$).

Medical history in our 130 patients showed only 4 patients with a history of recurrent urinary tract infections. Only one of these patients (aged 24 years) showed a slightly decreased creatinine clearance. In contrast, Morris et al. [1988] reported that 30% of their 17 WBS patients had urinary tract infections in their history. Two years later the same group [Morris et al., 1990] published a report on 13 adults with the syndrome 50% of whom tended to have urinary tract infections. Burn [1986] proposed the hypothesis that a late manifestation of renal diseases and urinary tract infections could be caused by hypercalcemia in early life. However, renal malformations were not mentioned in this study.

Biesecker et al. [1987] reported on a 19-year-old patient with bilateral multicystic kidneys and marked renal insufficiency. There is a second case with progressive renal insufficiency in the literature [Steiger et al., 1988]. This patient was on hemodialysis for 6 months and then underwent a successful renal transplantation. A primary malformation of the kidneys was not present. Decreased renal function in combination with nephrocalcinosis was described by Pober et al. [1993] in two children. In contrast, Stoermer et al. [1984] found no renal insufficiency in their series of WBS patients, a finding that is confirmed by our results. Renal artery stenosis and arterial hypertension are reported in a few cases [Ino et al., 1988; Stoermer et al., 1984; Ingelfinger and Newburger, 1991; and Pober et al., 1993]. We found mild renal artery stenosis in 8 of 18 patients who underwent cardiac catheterization. These patients received antihypertensive treatment except for one female infant age 6 months. Presumably the incidence of renal artery stenosis/narrowing is higher in WBS. This hypothesis is supported by the finding that hypoplasia of the ascending aorta and the aortic loop and even long aortic stenosis was seen in a relatively high number of patients [Wessel et al., 1994]. In addition, it has to be taken into account that renal artery narrowing/stenosis was not sought for systematically in a larger number of patients and that data on abdominal angiography are limited. However, it seems prudent to include abdominal angiographical evaluation in the procedure of cardiac catheterization of WBS patients. Upon initial diagnosis of WBS sonographic examination of the kidneys and urinary tract should be included in the standard diagnostic work-up.

REFERENCES

Biesecker LG, Laxova R, Friedman A (1987): Renal insufficiency in Williams syndrome. Am J Med Genet 28:131–135.

Bruns H-A (1968): Überraschende Befunde im Bereich des Harntraktes bei Kindern mit angeborenen Herzfehlern. Monatsschr Kinderheilkd 116:564–566.

Burn J (1986): Williams syndrome. J Med Genet 23:389–395.

Buyse ML (1990): "Birth Defects Encyclopedia." Dover, MD: Center for Birth Defects Information Services, Inc., pp 1779–1780.

Côté G, Jequier S, Kaplan P (1989): Increased renal medullary echogenicity in patients with Williams syndrome. Pediatr Radiol 19:481–483.

Dilts CV, Morris CA, Leonard CO (1990): Hypothesis for development of a behavioral phenotype in Williams syndrome. Am J Med Genet 6:126–131.

Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, Stock AD, Leppert M, Keating MT (1993): Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nature Genet 5:11–16.

Gorlin RJ, Cohen MM jr, Levin LS (1990): Syndromes of the head and neck. Oxford: Oxford University Press, pp 143–148.

Gosch A, Pankau R (1994): Social-emotional and behavioral adjustment in children with Williams-Beuren syndrome. Am J Med Genet 53:335–339.

Gosch A, Städing G, Pankau R (1994): Linguistic abilities in children with Williams-Beuren syndrome. Am J Med Genet 52:291–296.

Gruenwald P (1943): The normal changes in the position of the embryonic kidney. Anat Rec 85:163–176.

Ingelfinger JR, Newburger JW (1991): Spectrum of renal anomalies in patients with Williams syndrome. J Pediatr 119:771–773.

Ino T, Nishimoto K, Iwahara M, Akimoto K, Boku H, Kaneko K, Tokita A, Yabuta K, Tanaka J (1988): Progessive vascular lesions in Williams-Beuren syndrome. Pediatr Cardiol 9:55–58.

Jones KL (1988): "Smith's Recognizable Patterns of Human Malformation," 4th ED. Philadelphia: WB Saunders Company, pp 106–107.

Leiber B, Olbrich G (1990): "Die Klinischen Syndrome. Syndrome, Sequenzen und Symptomenkomplexe," 7th ED. Munich, Vienna, Baltimore: Urban & Schwarzenberg, pp 788–789.

Morris CA, Demsey SA, Leonhard CO, Dilts C, Blackburn BL (1988): Natural history of Williams syndrome: Physical characteristics. J Pediatr 113:318–326.

Morris CA, Leonhard CO, Dilts C, Demsey SA (1990): Adults with Williams syndrome. Am J Med Genet 6:102–107.

Page HL, Vogel JHK, Pryor R, Blount SG (1969): Supravalvular aortic stenosis. Am J Cardiol 23:270–277.

Pober BR, Lacro RV, Rice C, Mandell V, Teele RL (1993): Renal findings in 40 individuals with Williams syndrome. Am J Med Genet 46:271–274.

Sheih CHP, Liu M-B, Hung C-S, Yang K-H, Chen WY, Lin C-Y (1989): Renal abnormalities in school children. Pediatrics 84:1086–1090.

Steiger MJ, Rowe PA, Iinnes A, Burden RP (1988): Williams syndrome and renal failure. Lancet 2:804.

Steinhart JM, Kuhn JP, Eisenberg B, Vaughan RL, Maggioli AJ, Cozza TF (1988): Ultrasound screening of healthy infants for urinary tract abnormalities. Pediatrics 82:609–614.

Stoermer J, Olbing H, Hentrich F, Even K, Galal O, Bachmann J (1984): Das Syndrom der supravalvulären Aortenstenose (Williams-Beuren-Syndrom) in Verbindung mit Veränderungen der Niere und ableitenden Harnwege. Monatsschr Kinderheilkd 132:110–112.

Wessel A, Pankau R, Kececioglu D, Ruschewski W, Bürsch JH (1994): Three decades of follow-up of aortic and pulmonary vascular lesions in the Williams-Beuren syndrome. Am J Med Genet 52: 297–301.

Wesselhoeft H, Salomon F, Grimm T (1980): Spektrum der supravalvulären Aortenstenose: Untersuchungsergebnisse bei 150 Patienten mit Williams-Beuren-Syndrom und der der isolierten Form der supravalvulären Aortenstenose. Z Kardiol 69: 131–140.

Wiedemann HR, Kunze J (1995): "Atlas der klinischen Syndrome: Für Klinik und Praxis," 4th ED. Stuttgart, New York: Schattauer Verlag, pp 568–569.